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Simon E Barton

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Reducing the transmission of genital herpes

**Antiviral therapy is effective but should be used with safer sex practices and counselling**

Seven years ago, an editorial published in this journal called for studies to clarify the role of antiviral treatment in preventing the transmission of genital herpes. In the intervening years, seroprevalence studies in the United States have shown that the rate of infection with herpes simplex virus type 2 (HSV-2) has risen to 22%, whereas in Europe, rates between 4% and 44% have been reported. Support for an association between HSV-2 and HIV acquisition and transmission has increased, and anxiety about infecting their sexual partner is still among the top three concerns of people with genital herpes.

We know that antiviral treatment reduces asymptomatic transmission of HSV from genital mucosa, but until now we have not known whether this would translate into a real, clinically protective effect of condoms. None of the 141 HSV-2 discordant couples was less often transmitted in couples using condoms compared with placebo (relative risk 0.27, 95% confidence interval 0.27 to 0.99, P = 0.04). Genital herpes was less often transmitted in couples using condoms, but the benefit of valaciclovir was additional to the protective effect of condoms. None of the 141 individuals who took valaciclovir and used condoms for more than 90% of sexual encounters transmitted symptomatic genital herpes to their partner.

The rate of transmission in these monogamous HSV-2 discordant couples was very low, at under 5% over an eight month period, and we can speculate about reasons for this. Firstly, the study recruited women as the infected partners in 67% of couples, so most of the uninfected, seronegative partners were men. Men may be up to four times less susceptible to acquiring genital herpes than women (P = 0.006), so a low transmission rate was to be expected in this study. Secondly, all couples enrolled in the study were motivated to try to prevent the transmission of infection and were explicitly advised to abstain from sexual intercourse during recurrences and to use condoms for every sexual encounter. Such measures are central to the current behavioural approach to reducing the risk of transmission of genital herpes. In assessing the cost effectiveness of this intervention in data from a population with such a low rate of sexual HSV transmission, it may therefore be valuable to model these effects in populations at greater risk of transmission. These include people who are less motivated to follow behavioural advice or in scenarios where people change sexual partners often. Also covariables should be examined, such as concurrent HIV transmission, to inform decision making on the public health effectiveness of this intervention in targeted groups.

In clinical practice, which individuals would benefit most from suppressive antiviral treatment to reduce the transmission of genital herpes to a partner? HSV-2 infection often goes undiagnosed and may be asymptomatic. Individuals with asymptomatic HSV-2 infection, even if diagnosed, will not themselves benefit from the suppressive effect of continuous antiviral therapy. However, if the risk of transmission of infection is causing anxiety even patients who do not find their own symptoms bothersome may benefit from a period of antiviral suppression, which can be linked to behavioural sexual health advice. Patients who are already taking suppressive drugs may find it reassuring to know that the medication they are taking to control their own symptoms is also helping to protect their sexual partner.

In the United States the results of this study have led the Food and Drug Administration to approve a new indication for valaciclovir—the prevention of sexual transmission of HSV infection. However, it must be emphasised that these new data were obtained in immunocompetent, heterosexual couples who were motivated to enrol in a trial. How the benefits will be altered by adherence to treatment or whether antiviral suppression affords protection of HSV transmission in other scenarios—such as during pregnancy, across same sex...
relationships, or among individuals with HIV infection—
requires measured clinical judgment until further
studies are available. Furthermore, the vexed question
remains of whether the notable reduction in transmis-
ion provided by valaciclovir would be achieved by other
antiviral drugs, such as aciclovir or famiclovir, and if so,
at what dose? Without comparative data, individual pre-
scribing decisions in specific healthcare settings will
need to be made on the basis of factors including avail-
ability, potential adherence, and cost.

That no evidence of viral resistance was detected in
those individuals who became infected in this study is
reassuring. That some susceptible individuals did
become infected reinforces the message that valaciclovir
reduced the frequency of HSV reactivation, subclinical
shedding, and transmission of genital herpes, but it did
not eliminate it. Antiviral treatment is thus not a
substitute for other methods to control the spread of
sexually transmitted infections but an additional tool.
Patients should also be advised to continue using
condoms, practise safer sex, and inform their partner
about transmissible infections they have. The risk of
transmitting genital herpes will not be removed, but
patients can be assured that they are doing everything
they can to reduce the risk of infecting a loved one.

Simon E Barton clinical director
Dept of HIV/Gonitourinary Medicine, Chelsea and Westminster
Hospital, London SW10 9NH
(simon.barton@chelwest.nhs.uk)

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educational grants from GlaxoSmithKline. He has been
involved in clinical trials of aciclovir, valaciclovir, and famiclovir
in individuals with HSV infection.

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Schizophrenia: a genetic disorder of the synapse?
Glutamatergic synapses might be the site of primary abnormalities

Understanding the cause and pathogenesis of
schizophrenia remains one of the great
challenges in psychiatry. Progress has been slow, but one of the few certainties is that individual dif-
fferences in liability are predominantly genetic.1
This information has, however, not been useful neurobiologi-
cally because the genes themselves had not been identi-
fied. This situation is beginning to change, allowing a
reappraisal of existing hypotheses of pathogenesis.

Until recently the two leading hypotheses con-
cerned dopamine and neurodevelopment. The classic
dopamine hypothesis, which attributed schizophrenia
to a hyperdopaminergic state, arose from the ability of
dopaminergic drugs to induce a psychosis, and the
realisation that the potency of antipsychotic drugs is
proportional to their ability to block dopamine recep-
tors.2 Refinements of the hypothesis indicate a more
complex picture—increased dopaminergic transmis-
sion in the basal ganglia may underlie acute psychosis,3
but a prefrontal cortical dopamine deficit is associated
with neurocognitive impairments.4 The dopaminergic
changes are probably secondary to altered cortical
glutamatergic transmission,5 but compelling evidence
for a primary causative abnormality in neurotransmis-
sion does not exist.

Whatever the fundamental causes of schizophre-
nia, clinical, epidemiological and neuroimaging studies
clearly show that their influences are exerted from
early in life and well before the changes in neurotrans-
mission at the onset of acute psychosis.6,7 Given robust
findings that a number of brain regions are reduced in
size, the absence of any pathological evidence for neuro-
degeneration is also consistent, albeit by default, with a
neurodevelopmental model of schizophrenia.8

The positive findings from neuropathological studies
are not conclusive, but now reasonable evidence
exists for alterations in the cytoarchitecture of several
brain areas, notably the hippocampus, the prefrontal
cortex, and the dorsal thalamus where neurons,
dendrites, synapses, and oligodendrocytes are affected,9
Taken together, the findings imply an alteration in cor-
tical circuitry, which may represent the anatomical basis
of aberrant connectivity that has been inferred from
neuropsychological and functional imaging studies.

These and other hypotheses of schizophrenia have
been frustratingly vague, and although they provide
cues to proximal causes of symptoms, they do not
specify the causal molecular events. The situation, how-
ever, is now changing rapidly as several putative
susceptibility genes have been discovered. Evidence for
associations between DNA polymorphisms and schizo-
phrenia has been reported and, more importantly, rep-
licated for some of these genes.10 The degree of
agreement between studies sets these findings apart
from numerous other claims made on the basis of
single studies and makes it timely to consider how they
affect the biology of the disease.